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Cardiac Imaging

Is There a Referral Bias Against Catheterization of Patients With Reduced Left Ventricular Ejection Fraction?

Influence of Ejection Fraction and Inducible Ischemia on Post–Single-Photon Emission Computed Tomography Management of Patients Without a History of Coronary Artery Disease

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OBJECTIVES The objective of this work was to define the relationship between left ventricular perfusion/function measures and referral rates to catheterization and revascularization early after stress gated myocardial perfusion single-photon emission computed tomography (MPS).

BACKGROUND Although revascularization yields the greatest survival benefit in patients with low ejection fraction (EF) and extensive coronary artery disease, referral patterns to catheterization and revascularization after noninvasive testing are not well defined.

METHODS We identified 3,369 patients without previous myocardial infarction or revascularization who underwent exercise or adenosine stress MPS and who were followed-up (97% complete) for occurrence of early (<60 days) post–single-photon emission computed tomography (SPECT) revascularization. Multivariable logistic regression modeling was used to determine the association of various patient characteristics and test results with performance of catheterization and revascularization as separate end points.

RESULTS In the first 60 days after stress MPS, 445 catheterizations (13.2%) and 254 revascularizations (7.5%) occurred, including 140 coronary artery bypass graft surgeries (4.1%) and 114 percutaneous coronary interventions (3.4%). Both post-stress gated EF and percent of the myocardium ischemic by stress MPS were independent predictors of revascularization. Logistic regression revealed that the likelihood of catheterization increased with both increasing ischemia and decreasing EF (c-index = 0.94, chi-square = 590). Predicted referral rates to catheterization increased with decreasing EF except in patients with severe ischemia (>15% of myocardium), where rates decreased with decreasing EF. Similar modeling of revascularization (c-index = 0.94, chi-square = 329) revealed that the likelihood of revascularization increased with increasing ischemia but, in general, decreased with decreasing EF.

CONCLUSIONS Although post-SPECT referral to both catheterization and revascularization is driven by ischemia, EF has the opposite effect on these two outcomes. Further studies evaluating the appropriateness of these referral patterns are warranted. (J Am Coll Cardiol 2003;42: 1286–94) © 2003 by the American College of Cardiology Foundation

Numerous studies have evaluated the absolute and relative values of various markers for risk identification in patients with known or suspected coronary artery disease (CAD). The presence of extensive anatomic CAD, stress, or rest left ventricular (LV) dysfunction; exercise-induced electrocardiogram (ECG) changes; and the extent and severity of stress perfusion defects on myocardial perfusion single-photon emission computed tomography (MPS) all have been associated with an increased risk of cardiovascular mortality (1–10). Both randomized, clinical trials and large, observational data series have demonstrated that this risk, and its reduction by revascularization, increases with the extent of angiographic disease (1–3,11). The presence of LV dysfunction further identifies patients with an enhanced survival benefit as a result of revascularization (1), particularly in the presence of exercise-induced ECG changes (1,2). Using gated MPS, the combination of LV perfusion and function measures yield added prognostic information compared with either measure separately (6,7,12).

Previous studies have examined resource use early after MPS and the relationship between patient risk and physi-

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Abbreviations and Acronyms

CABG	= coronary artery bypass graft surgery
CAD	= coronary artery disease
ECG	= electrocardiogram/electrocardiographic
EF	= ejection fraction
LV	= left ventricle/left ventricular
MPS	= myocardial perfusion single-photon emission computed tomography
PCI	= percutaneous coronary intervention
SPECT	= single-photon emission computed tomography

cian action (13–17) and showed that referrals to catheterization and revascularization tracked closely with patient risk. However, observed and risk-adjusted referral rates to revascularization early after the use of stress MPS have not been examined in the context of both LV function and perfusion data. Our goal was to define the relationship between MPS-measured LV perfusion and function and subsequent resource use, as defined by early post-MPS referral to catheterization and revascularization.

METHODS

Study population. We identified 5,370 consecutive unique patients who underwent exercise or adenosine stress gated MPS between July 1992 and November 1998. Patients with previous myocardial infarction, revascularization, or known cardiomyopathy were excluded, leaving 3,481 patients (65% of initial cohort). Of these patients, 112 (3.4%) were lost to follow-up; hence, a final study population of 3,369 patients was used.

Imaging and stress protocol. Patients were injected intravenously at rest with thallium-201 (3.0 to 4.5 mCi) with dose variation based on patient weight. Rest thallium-201 single-photon emission computed tomography (SPECT) was initiated 10 min after injection of the radionuclide (14).

EXERCISE STRESS MPS PROTOCOL. Immediately after imaging, patients performed symptom-limited exercise treadmill testing using standard protocols. Exercise end points included physical exhaustion, severe angina, ventricular tachycardia, significant supraventricular arrhythmias, or significant exertional hypotension. At near-maximal exercise, a 25- to 40-mCi dose of technetium-99m sestamibi was injected and exercise continued for 1 min after injection (18).

ADENOSINE STRESS MPS PROTOCOL. Patients were instructed not to consume caffeine products for 24 h before stress MPS. After rest thallium-201 SPECT was completed, pharmacologic stress was performed using adenosine infusion (140 μg/kg/min for 5 to 6 min). Technetium-99m sestamibi (25 to 40 mCi) was injected at the end of the second or third minute of infusion (14). For patients who underwent exercise as an adjunct to adenosine infusion, low-level exercise treadmill testing was performed at 0% to 10% grade at 1 to 1.7 mph.

During both types of stress, 12-lead ECG recording was performed at each minute of stress with continuous monitoring of leads aVF, V_1, and V_5. Blood pressure was recorded at rest, at the end of each stress stage, and at peak stress. Maximal ST-segment change at 80 ms after the J point was assessed as horizontal, upsloping, or downsloping.

Post-stress gated SPECT acquisition protocol. Eight-frame post-stress gated SPECT was initiated 15 to 30 min after exercise or 15 to 60 min after adenosine stress. Circular or elliptical acquisitions were performed using a two-detector, three-detector, or single-detector camera, obtaining 60 to 64 projections over 180 projections for 35 s (thallium-201) or 25 s (technetium-99m sestamibi) per projection (18). The eight projection sets were summed to generate an "ungated" set for assessment of perfusion. Projection images were reconstructed into transaxial images using filtered backprojection. No attenuation or scatter correction was used. After automatic reorientation (19), gated short-axis tomograms were processed automatically to measure ejection fraction (EF) (20). The post-stress gated EF was used in all analyses.

Image interpretation. A semiquantitative visual interpretation was performed using 20 segments for each rest and stress image (18). Each segment was scored by consensus of two experienced observers by using a five-point scoring system (0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction of radioisotope uptake, and 4 = absence of detectable tracer uptake in a segment) as described previously.

Scintigraphic perfusion indices. Summed stress and rest scores were obtained by adding the scores of the 20 segments of the stress and rest images, respectively (21). The difference between the summed stress and rest scores was defined as the summed difference score, representing the amount of ischemia. These indices, incorporating the extent and severity of perfusion defects, were converted to percent of the myocardium manifesting stress, ischemic, or fixed defects by dividing the summed scores by 80, which is the maximum potential score (4×20), and multiplying by 100 (11).

Patient follow-up. Individuals who were blinded to the patients' test results performed follow-up by scripted telephone interview. The end point of the current study was referral to catheterization or revascularization early ($\leq$60 days) after stress MPS. This time point was selected because it has been shown to be a temporal threshold distinguishing referrals to revascularization made on the basis of the scan results ($\leq$60 days) as opposed to worsening of the patients' clinical status prompting intervention (>60 days) (22).

Statistical analysis. Baseline characteristics of patients were described in terms of mean $\pm$ 1 SD for continuous variables and frequencies for categorical variables. The former was compared using analysis of variance and the latter using a chi-square test for comparisons of discrete variables. A value of $p < 0.05$ was considered statistically significant.

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Table 1. Patient Characteristics and Univariate Predictors of Catheterization and Revascularization

		Referral to Catheterization		Referral to Revascularization	
		Chi-Squared	Odds Ratio	Chi-Squared	Odds Ratio
N	3,369 (100%)				
Exercise stress	2,146 (64%)	26.0*	0.59	4.0*	0.77
Male	1,742 (52%)	33.2*	1.83	29.8*	2.13
History catheterization	352 (10%)	9.0*	1.55	8.1*	1.67
Digoxin use	135 (4%)	1.2	1.30	0.1	0.91
Hypertension	1,630 (48%)	9.9*	1.38	17.2*	1.75
Diabetes mellitus	446 (13%)	34.3*	2.95	26.5*	2.22
Hypercholesterolemia	1,439 (43%)	0.1	0.97	0.3	1.09
Smoking	371 (11%)	2.7	1.28	0.7	1.18
Family history CAD	753 (22%)	6.4*	0.72	1.5	0.82
Anginal symptoms	1,575 (47%)	9.8*	1.37	25.6*	1.96
Abnormal rest ECG	1,837 (55%)	56.0*	2.28	23.4*	1.97
Age (yrs)	65 ± 13	45.2*	1.67	28.6*	1.03
% myocardium total	4.1 ± 8.6%	549.3*	1.18	439.3*	1.15
% myocardium ischemic	3.4 ± 7.2%	556.8*	1.23	442.8*	1.18
% myocardium fixed	0.7 ± 3.5%	77.4*	1.12	51.9*	1.09
Post-stress ejection fraction	62 ± 13	257.4*	0.94	152.4*	0.95
Year of stress myocardial perfusion SPECT study	1994: 150 1995: 400 1996: 876 1997: 1203 1998: 740	13.5*	0.81	3.7*	0.81

*$p < 0.05$.
CAD = coronary artery disease; ECG = electrocardiogram; SPECT = single-photon emission computed tomography.

MULTIVARIABLE MODELING. A logistic regression model was used to perform covariate adjustment to determine the association of patient characteristics and test results with performance of: 1) catheterization, and 2) revascularization as separate end points. Additional models were developed for coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI) as separate end points. Candidate variables for modeling are listed on Table 1.

Based on univariate analysis and clinical judgment, all factors known to influence these referral decisions were considered for entry into a logistic regression model within the constraints of overfitting (23,24). The threshold for entry of variables into all models was $p < 0.10$. Based on these models, risk-adjusted survival curves were determined. Care was given to examination of the assumptions of linearity and additivity (23,24). S plus 2000 (Mathsoft Inc., Cambridge, Massachusetts) using supplemental libraries was used for all analyses.

RESULTS

Patient characteristics. The baseline characteristics of patients in this study are shown in Table 1. Of the patients, approximately two-thirds underwent exercise stress, approximately one-half were male, and most had a history of hypertension, hypercholesterolemia, abnormal rest ECG, or anginal symptoms at the time of presentation. Small numbers of patients had a previous catheterization, were using digoxin, had diabetes mellitus, were smokers, or had a family history of premature CAD. The mean age was 65 ± 13 years, and the mean stress defect size was within the upper limits of normal and was predominantly reversible rather than fixed. The mean EF (62 ± 13%) was well within the normal range.

The distribution of EF was skewed toward higher values (<35%: 4%; 35% to 50%: 13%; >50%: 83%). The distribution of ischemia was also skewed toward having no ischemia; 66% of patients were not ischemic and 15%, 7%, 7%, and 5% were 1% to 5%, 6% to 10%, 11% to 20%, and >20% myocardium ischemic, respectively.

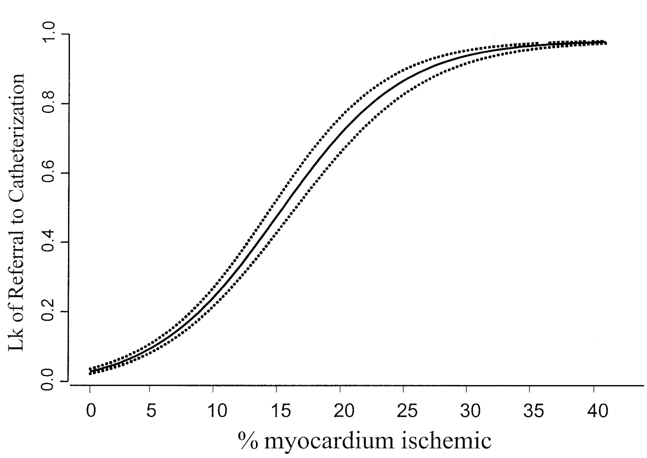

Figure 1. Univariate relationship between the likelihood (Lk) of catheterization referral and percent of the myocardium ischemic **(solid line)** with 95% confidence intervals **(dotted lines)**. Increase in likelihood, $p < 0.001$.

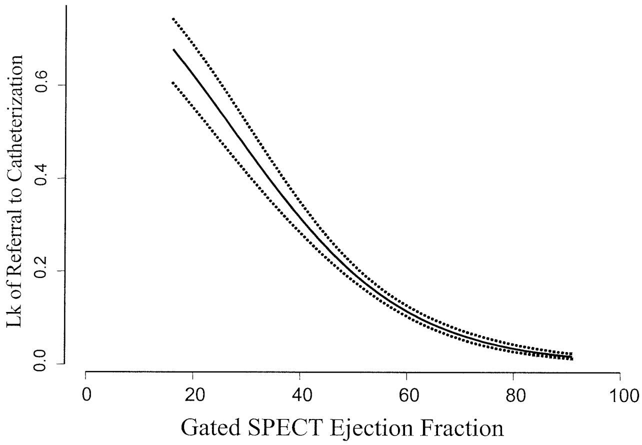

Figure 2. Univariate relationship between the likelihood (Lk) of catheterization referral and gated ejection fraction **(solid line)** with 95% confidence intervals **(dotted lines)**. Increase in likelihood, $p < 0.001$. SPECT = single-photon emission computed tomography.

Outcome events. In the first 60 days after stress MPS, 445 (13.2%) early catheterizations and 254 (7.5%) early revascularizations occurred, including 140 (4.1%) CABG and 114 (3.4%) PCI . The relationship between patient characteristics and likelihood of catheterization and revascularization based on single variable logistic regression models is shown in Table 1.

The best univariable predictors of catheterization and revascularization were percent of the myocardium total and percent of the myocardium ischemic. Each 1% increase in these variables resulted in an 18% and 23% increase in predicted catheterization and a 15% and 18% increase in predicted revascularization, respectively. Ejection fraction was the next most powerful predictor of both catheterization and revascularization. Each 1% decrease in EF resulted in a 6% and 5% increase in the likelihood of catheterization and revascularization, respectively. Male gender, the presence of diabetes mellitus, anginal symptoms, abnormal rest ECG, patient age, and percent of the myocardium fixed also were significant univariable predictors of catheterization and revascularization, as were, to a lesser extent, type of stress, and hypertension. Family history of CAD was also a significant univariable predictor of catheterization.

The univariable relationship between ischemia and the likelihood of revascularization is shown in Figure 1. The likelihood of revascularization was low in the setting of small amounts of ischemia but increased as a function of percent of the myocardium ischemic. This increase was greatest between 12.5% and 30% of the myocardium ischemic. The relationship between gated SPECT EF and the likelihood of revascularization (Fig. 2) demonstrates that as EF decreased, the likelihood of revascularization increased exponentially.

Multivariable modeling. The logistic regression model predicting early catheterization (Table 2) (c-index = 0.94, chi-square = 590) revealed that the most powerful predictor in this model was percent of the myocardium ischemic with a significant interaction between this variable and EF. Interestingly, the year the stress MPS study was performed was a significant predictor in this model, indicating the presence of a temporal change in practice patterns.

Observed referral rates to catheterization and revascularization as a function of categories of EF and percent of the myocardium ischemic (Table 3) revealed that in patients

Table 2. Logistic Regression Model Predicting Early Catheterization

Factor	Chi-Squared	β Coefficient	SE	p
Stress type	3.9	−0.3745	0.2612	< 0.09
All interactions	3.8			0.034
Male gender	11.4	−0.6920	0.2185	0.013
All interactions	7.4			0.024
Dyspnea	5.5	−0.3076	0.3441	0.097
All interactions	4.4			0.051
Year of SPECT study	4.0	0.1301	0.0650	0.038
Ischemic ECG response	5.6	0.4169	0.1761	0.035
% myocardium ischemic (factor + higher	477.9	−0.1609	0.1421	< 0.001
order factors)				< 0.001
All interactions	62.6			< 0.001
Nonlinear	165.0	0.4937	0.4815	
Age	16.7	0.2047	0.0602	< 0.001
Nonlinear	13.2	−0.0016	0.0005	< 0.002
Gated ejection fraction (factor + higher order factors)	85.6	−0.0898	0.0100	< 0.0001
All interactions	62.6			< 0.0001
Stress type × male gender	3.8	0.6125	0.3133	< 0.035
Male gender × dyspnea	4.4	0.9340	0.4449	< 0.051
SDS × gated ejection fraction	62.6	0.0169	0.0027	< 0.001
Nonlinear	23.2			< 0.001
Nonlinear interaction	23.2	−0.0453	0.0094	< 0.001
Total	590.5			< 0.0001

ECG = electrocardiogram; SE = standard error (of the β coefficient); SPECT = single-photon emission computed tomography.

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Table 3. Observed Referral Rates to Catheterization as a Function of EF and %Myocardium Ischemic

%Myocardium Ischemic		Observed Referral Rate to Catheterization n (%)	% of Patients Referred to Early Revascularization After Early Catheterization
<10%	EF ≤ 35%	39% (70)	30%
<10%	EF > 35%, <50%	11% (289)	36%
<10%	EF ≥ 50%	4% (2,560)	42%
10–20%	EF ≤ 35%	65% (48)	64%
10–20%	EF > 35%, <50%	61% (71)	58%
10–20%	EF ≥ 50%	63% (175)	61%
>20%	EF ≤ 35%	61% (26)	75%
>20%	EF > 35%, <50%	65% (65)	81%
>20%	EF ≥ 50%	77% (64)	73%

EF = ejection fraction.

with <10% myocardium ischemic, referral rates to catheterization decreased with increasing EF. However, for patients with 10% to 20% and >20% myocardium ischemic, no differences in referral rates to catheterization were noted as a function of EF.

The relationship defined by the percent of the myocardium ischemic/EF interaction (Fig. 3) reveals a marked increase in the likelihood of referral to catheterization with increasing amounts of ischemia, with the maximal slope of this increase occurring between 5% to 15% of the myocardium ischemic in patients with normal EF. In patients with >10% of the myocardium ischemic, the likelihood of this referral decreased as a function of decreasing EF. However, patients with low EF (<45%) and small amounts of percent of the myocardium ischemic (<10%) had an increasing likelihood of referral to catheterization with decreasing ischemia and decreasing EF. Further, this model also revealed that the year the index SPECT study was performed influenced the likelihood of referral to catheterization, with progressive increases each year from 1994 to 1998.

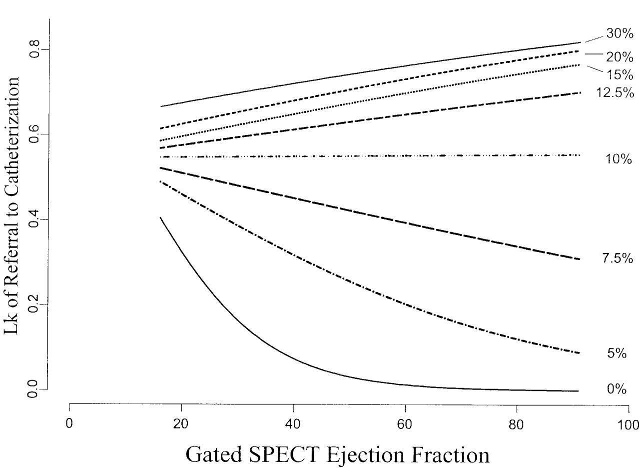

Figure 3. Relationship between gated ejection fraction and percent of the myocardium ischemia with respect to prediction of likelihood (Lk) of catheterization referral based on logistic regression model. Results are shown for percent of the myocardium ischemia values of 0%, 5%, 7.5%, 10%, 12.5%, 15%, 20%, and 30%. SPECT = single-photon emission computed tomography.

The logistic regression model predicting revascularization (Table 4) (c-index = 0.94, chi-square = 329) revealed percent of the myocardium ischemic as the most powerful predictor with a significant interaction between this variable and EF. The contribution of percent of the myocardium fixed was significant but smaller. The relationship defined by the percent of the myocardium ischemic/ EF interaction (Fig. 4) indicates that in patients with normal EF, a marked increase in the likelihood of revascularization occurred with increasing amounts of ischemia. The slope of this increase was maximal between 5% to 15% of the myocardium ischemic and plateaued beyond that point. Importantly, for values of EF below 50%, a linear relationship was present. This relationship was further investigated by examining CABG and PCI as separate end points. The logistic regression model predicting CABG (c-index = 0.94, chi-square = 204) included anginal symptoms, ST-segment changes with stress, gated EF, percent of the myocardium fixed, and percent of the myocardium ischemic. The latter was again the most powerful predictor (>80% of overall chi-square), interacted powerfully with gated EF, and was modeled non-linearly. The relationship defined by the percent of the myocardium ischemic/EF interaction for this model is shown in Figure 5. In contrast to the likelihood of referral to revascularization (Fig. 4), this relationship demonstrates an increase in the likelihood of referral to CABG as a function of increasing percent of the myocardium ischemic with a small *increase* in likelihood as a function of decreasing EF. The logistic regression model predicting PCI (c-index = 0.90, chi-square = 223) included hypertension, anginal symptoms, gated EF, and percent of the myocardium ischemic, with the latter interacting with gated EF and being the most powerful individual predictor in the model (>80% overall chi-square). The relationship defined by the percent of the myocardium ischemic/EF interaction is shown in Figure 6. There was a low likelihood of referral to PCI in the setting of an EF <35% irrespective of the amount of ischemia present. In the setting of an EF 35% to 50%, the likelihood of revascularization was low when the amount of ischemia was small to moderate but rose when the amount of ischemia was large (>15% of the myocardium ischemic). When EF was >50%, the likelihood of referral to PCI increased steeply for patients with percent of the myocardium ischemic 15% to 30% and reached a plateau in patients with percent of the myocardium ischemic >30%.

Multivariable modeling in patients with ischemia and reduced EFs. We performed a subgroup analysis in a subgroup of 273 patients with EF <50% and >5% of the myocardium ischemic. These patients had 154 early catheterizations on follow-up. The logistic model most predictive of referral to catheterization included stress type, patient gender, the year the SPECT study was performed, percent

Table 4. Logistic Regression Model Predicting Early Revascularization

Factor	Chi-Squared	β Coefficient	SE	p
Hypertension	4.3	0.3477	0.1671	0.037
Anginal symptoms	12.8	0.6089	0.1703	< 0.0005
Gated ejection fraction (factor + higher order factors)	14.1	−0.0574	0.0170	< 0.003
All interactions	14.1			
ST-segment depression	7.4	0.1916	0.0702	< 0.001
%myocardium fixed	11.8	0.0652	0.0190	< 0.007
%myocardium ischemic (factor + higher order factors)	269.5	0.0908	0.2005	< 0.0001
All interactions	14.1			< 0.001
Nonlinear	101.7	−0.0625	0.6240	< 0.0001
Gated ejection fraction × % myocardium ischemic (factor + higher order factors)	14.1	0.0128	0.0037	< 0.001
Nonlinear	9.2			0.0024
Nonlinear interaction	9.2	−0.0361	0.0119	0.0024
Total	329			< 0.0001

SE = standard error (of the β coefficient).

of the myocardium ischemic (modeled nonlinearly), and EF, as well as an interaction between percent of the myocardium ischemic and EF. The three-dimensional relationship among percent of the myocardium ischemic, EF, and likelihood of catheterization was unchanged from that shown in Figure 3.

Results of catheterization in patients with severe stress MPS abnormalities. To better understand referral patterns in our cohort, we examined catheterization results in patients with ≥10% of the myocardium ischemic and EF ≤35% who underwent catheterization but were not referred to revascularization. Of the 74 patients who met these criteria, 47 (63%) were referred to early catheterization and 27 were not. We compared these two groups with respect to clinical, demographic, stress test, perfusion, and EF characteristics and found no significant differences or even trends toward differences between these groups. Of the 47 patients in the former group, 68% (32 of 47) were referred to early revascularization. With respect to the 15 patients who underwent catheterization but were not referred to revascularization, catheterization reports were available for 9 patients. Catheterization in these patients revealed that 3 (33.3%) patients had no CAD, 2 (22.2%) had single-vessel CAD, 2 (22.2%) had two-vessel CAD, and 2 (22.2%) had three-vessel CAD. Of the 74 patients with ≥10% of the myocardium ischemic and EF ≤35% referred to above who underwent catheterization, 27 (37%) were not referred to catheterization.

DISCUSSION

In the current study, we sought to determine the relationship between ischemia by stress MPS and post-stress EF with respect to the likelihood of referral to early catheterization and revascularization. With respect to both percent of the myocardium ischemic and EF as univariable predictors, increasing amounts of abnormality were associated with increasing likelihood of referral to catheterization; this

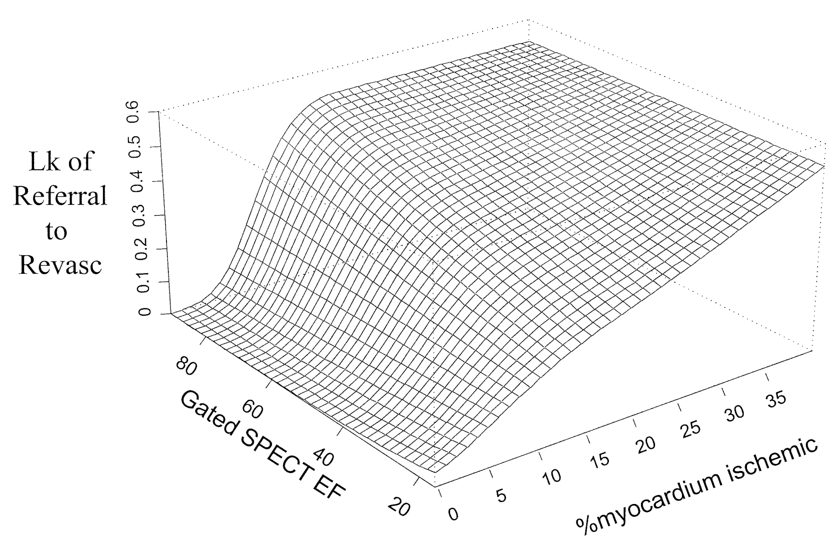

Figure 4. Relationship between gated ejection fraction (EF) and percent of the myocardium ischemia with respect to prediction of likelihood (Lk) of revascularization (Revasc) referral based on logistic regression model. Increase in likelihood, $p < 0.0001$. SPECT = single-photon emission computed tomography.

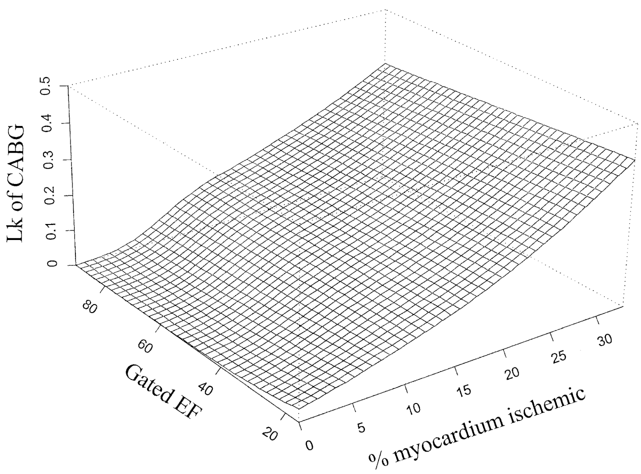

Figure 5. Relationship between gated ejection fraction (EF) and percent of the myocardium ischemia with respect to prediction of likelihood (Lk) of coronary artery bypass graft surgery (CABG) referral based on a logistic regression model. Increase in likelihood, $p < 0.0001$.

relationship was steeper in the setting of moderate and severe rather than mild abnormalities. Logistic regression modeling of referral to both catheterization and revascularization yielded robust models (c-indices both 0.94). Both models indicated that the majority of referrals to either procedure could be explained by percent of the myocardium ischemia with an interaction present between percent of the myocardium ischemic and EF for both end points. Referral rates to catheterization increased with decreasing values of EF in the setting of no (<5% of the myocardium ischemic) or mild to moderate amounts of ischemia (5% to 15% of the myocardium ischemic), but this pattern was reversed in patients with severe ischemia (>15% of the myocardium ischemic) wherein predicted referral rates to catheterization decreased with decreasing EF. Referral rates to revascularization increased markedly with increasing amounts of ischemia, plateauing beyond 15% of the myocardium ischemia, and demonstrated a mild decrease in referral rates with decreasing EF that was quantitatively not as significant as that found in the referral to catheterization model. Although referral to revascularization seemed to be in proportion to the anticipated risk in these patients, catheterization was the rate-limiting step in the evaluation of these patients and was significantly influenced by an EF-related referral bias.

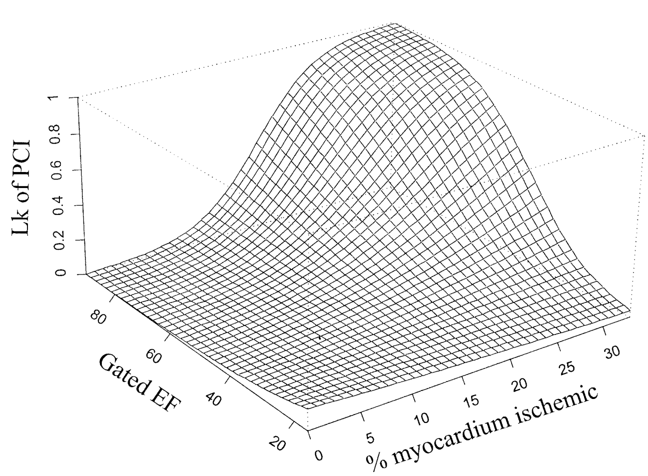

Figure 6. Relationship between gated ejection fraction (EF) and percent of the myocardium ischemia with respect to prediction of likelihood (Lk) of percutaneous coronary intervention (PCI) referral based on logistic regression model. Increase in likelihood, $p < 0.0001$.

Comparison of the current study to previous studies: post-stress MPS resource use. A number of previous studies have demonstrated the preeminent role of MPS-demonstrated ischemia and post-SPECT referral rates to catheterization and revascularization (14–17). Our group showed that in patients without previous CAD, this is the case in all (low, intermediate, and high) clinical risk subsets (14). The current study supports these previous findings and extends them by demonstrating the positive effect of post-stress EF on catheterization referral in the setting of little or no ischemia but its negative effect on this referral in the setting of extensive ischemia. Ejection fraction tended to adversely affect referral to revascularization, but this was quantitatively less significant than the effect on catheterization referral. With respect to referral to CABG, percent of the myocardium ischemic but not EF influenced referral rates. Because the former and not the latter defined potentially salvageable myocardium, this referral pattern is probably appropriate and reflects an attempt to intervene in proportion to potential benefit. Of concern, however, is that PCI referral patterns suggest that a referral bias is present such that patients with compromised LV function may be selectively under-referred to PCI.

Previous studies: risk as a function of CAD extent and LVEF. Previous studies have shown that the combination of LV perfusion and function measures yield increased prognostic information compared with either of these two measures separately (6,7,12). We have previously shown that with respect to annualized cardiac death risk in medically treated patients, both patients with EF >50% and a large amount of ischemia, as well as patients with EF 30% to 50% and mild or moderate ischemia, were at intermediate risk (2% to 3%). Also, patients with mild or moderate ischemia and EF >50% were at low risk (<1%) (25). Further, patients with EF <30% were at high risk (>4%) irrespective of ischemia amount. In light of these findings, the current study indicates that post-SPECT referral to catheterization in patients with low EF is disproportionately low relative to their risk. Recent studies have extended these findings and shown that the survival benefit associated with revascularization increases as a function of percent of the myocardium ischemic (11), even in the setting of a reduced EF (12).

Is there a referral bias against catheterization of patients with low EF and significant inducible ischemia? To classify a pattern of clinical care as "bias," a pattern of referral contrary to accepted, recommended, or optimal practice must be shown. Numerous studies have shown that risk—and survival benefit with revascularization—increases in the setting of low EF (1,3,12). As discussed in the preceding text, low gated SPECT EF is associated with greater risk and a potential survival benefit if ischemia is present (7,12). Hence, the failure of referral rates to catheterization to increase in proportion to patient risk would appear to potentially be less than optimal practice and may thus be considered a referral bias.

Impact of referral bias on assessment of prognostic value. With respect to diagnostic testing, the preferential referral of patients with positive test responses to a gold standard results in a post-test referral bias when the sensitivity and specificity of this test are subsequently examined (26). Similar referral biases can occur with respect to prognostic testing. Observational studies assessing the prognostic value of noninvasive testing censor patients undergoing early post-testing revascularization because of the relationship between this revascularization and the test results (22,26). We have previously hypothesized that with increasing physician acceptance of stress MPS and the strong dependence of post-MPS revascularization referral on these results, a post-test referral bias may develop that results in an underestimation of the test's prognostic value as a result of the revascularization (and censoring) of the highest risk patients (9,26,27).

The current study suggests that this source of post-test referral bias may adversely affect the observed prognostic value of stress-induced ischemia but not EF. In this study, the likelihood of referral to revascularization was positively affected by ischemia but only minimally affected by the EF, especially in patients with severe ischemia, thus adversely affecting the observed relationship between risk and ischemia, but less so the relationship between risk and EF. The previous results of Sharir et al. (7), that post-stress gated SPECT EF yields greater prognostic value than perfusion data, may have been due, in part, to this referral bias. In the future, these types of studies may benefit from an analytic approach that incorporates (and adjusts for) this referral bias.

Study limitations. STATISTICAL AND CLINICAL. The problems associated with the use of multivariable techniques applied to observational data to adjust for differences in baseline characteristics are well described (23,24,26). Nonetheless, this remains an observational study with all the flaws inherent in its design. The impact of various biases, missing covariates, and the limits of single-site data from a center whose referral and testing patterns may be unique all limit the reliability and generalizability of the current results. In addition, as single-center data, the interpretive and/or referral patterns reported may not be generalizable. Finally, although this study is well-powered overall, certain conclusions of this study are based on a relatively small number of patients.

TECHNICAL. Scintigraphic studies in the current work were interpreted by experienced observers using a standardized, semiquantitative approach to visual interpretation that we have developed and have documented to be highly reproducible (28,29). These form the basis for existent quantitative analysis programs that have been shown to correlate strongly with those of quantitative analysis (28,29). All EF data reported in the current study were obtained as a post-stress measurement in which the acquisition was initiated as early as 15 min (exercise stress) and as late as 60 min or more (adenosine stress) post-stress. Importantly, although the type of stress performed was a potential source of variation, it was not a significant predictor of revascularization in the logistic model for any of the end points we examined.

Conclusions. Although post-SPECT referral to catheterization and revascularization is primarily driven by the extent and severity of ischemia on gated stress MPS, referral rates are less affected by EF in patients with ischemia. Hence, a post-SPECT referral bias is present with respect to referral to catheterization, resulting in a relative undercatheterization of patients with low EF and significant ischemia. Further studies evaluating the appropriateness of these referral patterns would be warranted.

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